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Commentary

Issues in the Risk Assessment of Chromium

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Although hexavalent chromium is well established as a human carcinogen by the inhalation route, there are significant uncertainties in the quantitative estimation of cancer risk. One of the important uncertainties is the assumption that the carcinogenic potency, determined under conditions of occupational exposure where most workers were cigarette smokers, applies to the nonsmoking individual in the general population. There is substantial evidence that carcinogenicity is a function of the rate of cell turnover in the target tissue. The chromate worker would be expected to have a relatively high rate of cell proliferation in the bronchial mucosa due to airborne irritants and smoking. The potency of chromium might therefore be relatively high under conditions of occupational exposure. This problem in quantitative risk assessment applies equally well to another important indoor pollutant, radon.

From the standpoint of the hazard evaluation portion of the carcinogen risk assessment process, we are better off in the case of chromium than with most of the agents that have had to be dealt with by regulatory agencies. Chromium is thoroughly established as a human carcinogen and is regarded as such by the International Agency for Research on Cancer (*1*), the Environmental Protection Agency (*2*), and the World Health Organization (*3*). This judgment is based on over 40 epidemiological studies. The hexavalent form of chromium has also been established as a carcinogen in animals (*4*), and this form of chromium is also genotoxic in a variety of short-term genetic bioassays (*5,6*). There is general acceptance that it is only the inhaled form of hexavalent chromium that is carcinogenic, and it affects only the lung; ingested chromium of any form does not constitute a cancer hazard. So, there is no question that inhaled hexavalent chromium should be treated as a human carcinogen.

From the standpoint of quantitative risk assessment, there are the same uncertainties in the character of the dose-response relationships at low levels of exposure that are common to all other carcinogens. Chromium does have some quantitative exposure data in relation to cancer response. Thus, the uncertainties in the extrapolation of animal responses to humans that apply to agents whose evidence for carcinogenicity comes only from animal studies is less important for chromium. A significant issue is the applicability of lung cancer responses that occur in the occupational setting to the estimation of risks from exposure of the general population in their homes. The problem is comparable to the situation with radon gas in homes. Like chromium, the evidence for the carcinogenicity of radon for the lung currently comes only from occupational groups, namely, uranium miners. Radon is also an unequivocal lung carcinogen for humans, based on a number of epidemiological studies (*7*). Radon is carcinogenic for the lung in animals, and there is evidence for the genotoxicity of radon from a variety of genetic bioassays.

The major uncertainties in extrapolating occupational lung cancer responses in worker populations to indoor exposure of the general population are those related to age, sex, and cigarette smoking. Men constituted the entire worker populations in the uranium mines and the chromate industry, and most were cigarette smokers. There are very few data comparing the lung cancer responses to carcinogens in men and women, but given the sharply rising incidence of lung cancer in women associated with the corresponding increase in the number of women who are smokers, the differences in responsiveness between men and women are probably not large.

There is one possibly major factor that differentiates the smoking miner or chromate worker from a nonsmoking member of the general population and that is the rate of cell proliferation of the epithelial cells in the

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mucosa of the larger bronchi where most of the cancers arise. These cells are the targets for cancer development from both radon and chromium. The epithelial cells of the bronchial mucosa have one of the lowest rates of turnover in any of the body tissues (*8*). It is well established that cell proliferation is an essential factor in the carcinogenic process. Cells in tissue culture require several divisions after exposure to ionizing radiation to fix neoplastic transformation (*9*). Benzo[*a*]pyrene administered by intratracheal injection does not produce tracheal tumors unless the trachea is traumatized by the injection needle, thereby inducing cell proliferation (*10*). Similarly, the induction of bronchiolar tumors in the hamster lung by the instillation of radioactive polonium in the lung is markedly enhanced by subsequent injections of saline, which induce cell proliferation (*11*). In another proliferatively static tissue, the liver, urethane administered to the adult mouse does not induce tumors unless there is stimulation of cell proliferation by partial hepatectomy (*12*). Very young animals whose livers are proliferating relatively rapidly as part of the growth process are much more susceptible to tumor formation than adult rats (*13*). Similarly, tumor induction in the rapidly growing newborn rat by ionizing radiation is more effective than in the adolescent rat by a factor of three (*14*). Tumor induction in the nasal mucosa of the rat by the inhalation of formaldehyde does not occur at doses that do not increase the normally very low level of cell proliferation in that tissue (*15*). Wounding of the mouse skin after initiation by a small dose of carcinogen, a procedure which markedly increases cell proliferation, is an effective promoting factor (*16*). A characteristic feature of promoting agents is their ability to increase the level of cell proliferation (*17*). It is possible that a measure of effective carcinogen dose would be the target tissue dose at the time of cell replication, and hence the effective carcinogen dose would be proportional to cell replication rates for equal target cell carcinogen doses.

Chronic inhalation of cigarette smoke, in common with other irritants, causes the respiratory mucosa to change from its normal relatively nonproliferative secretory and ciliated pattern to one of squamous metaplasia, which has a higher than normal proliferative rate (*18*). The normally heavy atmospheric loading of irritating dusts, gases, and fumes in uranium mines and chromate plants would be expected to cause squamous metaplasia even in the absence of cigarette smoking. Hence, a possibly important difference between the cigarette-smoking chromate worker and uranium miner would be the higher proliferation rates in the bronchial mucosa than in the nonsmoking member of the general adult population who does not work in irritant atmospheres. For the latter population, exposure to indoor pollution from chromium and radon night be less hazardous than in uranium miners and chromate workers for equivalent exposure. In fact, the risks experienced by uranium miners and chromate workers may be more relevant to the growing individual who has a relatively high proliferation rate in the bronchial mucosa.

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